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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/905,056 | 07/12/2001 | Avi Ashkenazi | 10466/81 | 2902 |

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| EXAMINER | |
|---|---|
| KEMMERER, ELIZABETH | |
| ART UNIT | PAPER NUMBER |
| 1646 | |

DATE MAILED: 02/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/905,056 | ASHKENAZI ET AL. | |
| | Examiner | Art Unit | |
| | Elizabeth C. Kemmerer, Ph.D. | 1646 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *39-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *39-44,47,48,50 and 51* is/are rejected.

7)☐ Claim(s) *45,46 and 49* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 July 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

***Status of Application, Amendments, And/Or Claims***

The preliminary amendments of 12 July 2001 (Paper Nos. 5 and 6) and 27 August 2002 (Paper No. 10) have been entered in full. Claims 1-38 are canceled. Claims 39-51 are under examination.

The application is in compliance with the sequence rules, 37 CFR 1.821-1.825.

***Priority given to some parent cases but not others:***

According to the priority statement of 27 August 2002, Applicant claims priority to several U.S. non-provisional, PCT applications and U.S. provisional applications. Based on the information given by applicant and an inspection of the patent applications, the examiner has concluded that the subject matter defined in this application is supported by the disclosure in U.S. patent application serial number 09/665350, filed 18 September 2000; PCT application PCT/US00/04414 (published as WO 200104311 A1) filed 22 February 2000; and PCT application PCT/US98/19330 (published as WO 199914328), filed 16 September 1998 but is not supported by any of the others for the following reasons. All of the applications disclose the DNA and amino acid sequence of PRO331. However, only the three priority applications listed above disclose an enabled use for PRO 331, namely, that it inhibits VEGF stimulated proliferation of endothelial cells or induces apoptosis in endothelial cells. Accordingly, the subject matter defined in claims 39-51 has an effective filing date of 16 September 1998.

Should the applicant disagree with the examiner's factual determination above, it is incumbent upon the applicant to provide the serial number and specific page number(s) of any parent application filed prior to 16 September 1998 which specifically supports the particular claim limitation for each and every claim limitation in all the pending claims which applicant considers to have been in possession and fully enabled of prior to 16 September 1998.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 39-44, 47, 48, 50 and 51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The protein identified as PRO331 is a soluble protein, and is not disclosed as being expressed on a cell surface. Accordingly, the limitation that the claimed protein comprises an "extracellular domain" (for example see claim 39 parts (c) and (d)) is indefinite, as the art does not recognize soluble proteins as having such domains. Further, if the protein had an extracellular domain, the recitation of "the extracellular domain"..."lacking its associated signal sequence" (claim 39, part (d), for example) is indefinite as a signal sequence is not generally considered to be part of an extracellular domain, as signal sequences are cleaved from said domains in the process of secretion from the cell.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39-44, 47, 48, 50 and 51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide having at least 80% amino acid sequence identity to the polypeptide of SEQ ID NO:292 or the mature form thereof (approximately amino acids 45-640), which isolated polypeptide has the activity of inhibiting VEGF stimulated proliferation of endothelial cells, or inducing an immune/inflammatory response, or inducing apoptosis in endothelial cells, does not reasonably provide enablement for a polypeptide not identical to at least the mature form of SEQ ID NO:292 which does not have a specific activity limitation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn to a polypeptide having at least 80% amino acid sequence identity to the polypeptide of SEQ ID NO: 292 or the extracellular domain thereof (approximately amino acids 45-640), both referred to as PRO331. There is no functional limitation in the claims. Applicants have taught the polypeptide consisting of SEQ ID NO: 292, as well as the putative signal sequence (approximately amino acids 1-44 of SEQ ID NO: 292, Figure 104). This polypeptide was shown to have the activity of inhibiting VEGF stimulated proliferation of endothelial cells (pp. 204-205) or inducing an immune/inflammatory response (pp. 210-211) or inducing apoptosis in endothelial cells (p. 216).

The claim encompasses an unreasonable number of inoperative polypeptides, which the skilled artisan would not know how to use. While the specification suggests that the polypeptide of SEQ ID NO: 292 is a leucine-rich, decorin-like polypeptide, what receptor it binds or what leucine-rich, decorin-related function it possesses aside from inhibiting VEGF stimulated proliferation of endothelial cells or inducing apoptosis in endothelial cells is undisclosed. Since PRO331 it is a secreted protein, it would be expected that the mature form would be sufficient for function in the absence of the secretory signal. The functional domain of a leucine-rich protein like decorin is the mature form. As opposed to the claims, what is disclosed about PRO331 is narrow: a single polypeptide with three disclosed functions and no other obvious specific functions. The art prior to the effective filing date of 16 September 1998 is silent with respect to PRO331. Regarding leucine-rich proteins like decorin, the art recognizes that there is great functional diversity among proteins in this class, and that the functions of

decorin are not yet well known (see art reviewed at pp. 30-31 of the specification; Kresse et al., 2001, J. Cell. Physiol. 189:266-274, esp. pp. 268-270). Therefore, the skill in the leucine-rich protein art is not high because there are a several classes of leucine-rich proteins and within classes, such as decorins, there is great diversity and uncertainty of function.

There are no working examples of polypeptides less than 100% identical to the polypeptide SEQ ID NO:292 or the mature form thereof. There are four examples in which PRO331 was alleged to have activity: inhibition of VEGF stimulated endothelial cell proliferation (EXAMPLE 66, pp. 204-205); stimulation and inhibition activity in mixed lymphocyte reactions (MLR) assays (EXAMPLE 74, pp. 208-209), stimulation of immune response/inflammation (EXAMPLE 77, pp. 210-211), induction of apoptosis in endothelial cells (EXAMPLE 86, p. 216). The MLR results are contradictory and do not provide the skilled artisan with guidance for how to use the polypeptide. The results of EXAMPLES 66, 77 and 86 do. The skilled artisan would not know how to use non-identical polypeptides on the basis of teachings in the prior art or specification unless they possessed the activities of inhibiting VEGF stimulated proliferation of endothelial cells, or inducing an immune/inflammatory response, or inducing apoptosis in endothelial cells, as disclosed in the instant specification. While the specification generally describes properties of leucine-rich proteins, it is acknowledged that such proteins are diverse in function and structure (pp. 30-31 of specification; also Kresse et al., *supra*). The specification does not provide guidance for using polypeptides related to (*i.e.,* 80%-99% identity) but not identical to at least amino acids 45-640 of SEQ ID

NO: 292 which do not have one of the specific disclosed activities shown for PRO331. The claims are broad because they do not require the claimed polypeptide to be identical to the disclosed sequence and because the claims have no functional limitation.

For these reasons, which include the complexity and unpredictability of the nature of the invention and art in terms of the diversity of leucine-rich proteins and lack of knowledge about function(s) of encompassed polypeptides structurally related to SEQ ID NO: 292, the limited working examples of PRO331 polypeptide, the lack of direction or guidance for using polypeptides that are not identical to at least the extracellular domain of SEQ ID NO: 292, and the breadth of the claims for structure without function, it would require undue experimentation to use the invention commensurate in scope with the claims.

Claims 39-44, 47, 48, 50 and 51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to polypeptides having at least 80%, 85%, 90%, 95% or 99% sequence identity with a particular disclosed sequence. The claims do not require that the polypeptide possess any particular conserved structure, or other distinguishing

feature. Thus, the claims are drawn to a genus of polypeptides that is defined by sequence identity.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the claim that is sufficiently disclosed is a partial structure in the form of a recitation of percent identity. The specification does not identify any particular portion of the structure that must be conserved, nor does it provide a disclosure of structure/function correlation. The distinguishing characteristics of the claimed genus are not described. The only adequately described species is a polypeptide comprising SEQ ID NO: 292. No active variants are disclosed. Accordingly, the specification does not provide adequate written description of the claimed genus.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the

encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 292, or the mature form thereof, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

***Claim Objections***

Claims 45, 46 and 49 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (703) 308-2673. The examiner can normally be reached on Mon. - Thurs., 6:30 to 4:00, and alternate Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne L. Eyler, Ph.D. can be reached on (703) 308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

ECK
February 11, 2003

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER